Can’t I Just Take a Pill For It?

BY REGINA PATRICK, RPSGT, ASSOCIATE EDITOR

Upon receiving a diagnosis of sleep apnea and on being told that the most effective treatment for it is a machine that blows air through the nose all night, patients often ask with timorous hope: “Can’t I just take a pill for it?”

The answer has been a reluctant “no” despite scientists’ efforts for many years to find drugs that could act as an “apnea pill.” But latest efforts are encouraging and this answer may soon be changed to a “yes.” Drugs that target the neurological aspect of respiration have had the most success in reducing apnea. Of particular interest are drugs that affect the transmission of the neurotransmitter serotonin.

Serotonin is stored within the terminal of a neuron’s axon. When an impulse stimulates the neuron, serotonin is released outside of the axon. The neurotransmitter travels across a small gap (the synaptic cleft) before reaching and attaching to receptor sites on the next (i.e., post-synaptic) cell.

A small amount of the serotonin, however, is reabsorbed from the synaptic cleft back onto receptors of the cell (i.e., presynaptic cell) which released the serotonin. This process of reabsorption is called reuptake.

If the reuptake process is blocked, increased levels of serotonin remain in the synaptic cleft and the stimulatory effects of serotonin are increased. It is the increase in one effect — stimulation of the nerves that supply the upper airway dilator muscles — that may provide a drug treatment for sleep apnea.

The serotonergic pathway to the upper airway dilator muscles begins in the caudal raphe nuclei. Fibers from the caudal raphe nuclei relay impulses to the hypoglossal nuclei (which are the origin for the hypoglossal nerves) in the medulla. The impulse then travels down the hypoglossal nerves which exit the medulla and make a pathway toward the jaw. The nerves break into several branches in order to innervate the tongue and various upper airway muscles.

The upper airway dilator muscles (such as hypoglossus and the genioglossus muscles) keep the airway open during inspirations. If the upper airway muscles are weak or do not accurately work in unison to keep the airway open, the airway can collapse on inspirations and cause apnea.

In a 1996 study on English bulldogs, Sigrid C. Veasey et al. theorized that if the stimulatory effect of serotonin on the upper airway nerves keeps the upper airway open then administration of drugs that attach to (i.e., antagonize) receptors activated by serotonin would block the neurotransmitter from stimulating the nerves and allow the upper airway to collapse. They used ritanserin and methysergide to test this theory and also to determine which serotonin receptors are specifically involved in stimulating upper airway nerves. Currently, scientists know of...
The serotonergic pathways of respiration in order to treat apnea and are beginning to develop specially-designed drugs such as the serotonin type 2 5-HT2 receptor antagonist mianserin specifically to reduce sleep apnea. Interestingly, L-tryptophan did not reduce central apneas. Nevertheless, Schmidt concluded that an impairment in tryptophan-serotonin metabolism could be responsible for sleep apnea.

Since then, scientists have attempted to reduce sleep apnea with drugs that alter serotonin transmission such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and serotonin receptor antagonists. Success with these drugs has been inconsistent (i.e., different studies give conflicting results about a particular drug) or disappointing (e.g., a drug acts differently in REM sleep than in nonREM sleep). For example:

Brownell et al. tested the ability of the tricyclic antidepressant protriptyline to reduce sleep apnea. (Tricyclic antidepressants block the reuptake of serotonin as well as other neurotransmitters which results in increased levels of the neurotransmitters in the synaptic cleft). Brownell found that protriptyline did not reduce the amount of apnea or the duration of apnea except during REM sleep.

Hanzel et al.5 compared protriptyline with the SSRI fluoxetine in 12 subjects (SSRIs block the reuptake of serotonin but not other neurotransmitters). Unlike Brownell et al. who found that protriptyline reduced apnea in REM sleep, Hanzel et al. found that both protriptyline and fluoxetine significantly reduced apneas and hypopneas in nonREM sleep.

In a 1998 study on rats, Carley and Radulovacki found that two doses (.05 mg/kg and 5 mg/kg) of the benzodiazepine diazepam reduced sleep apnea by 50 percent in nonREM but not REM sleep. They postulate that two different processes may explain this difference. That is, the process which results in apneas during REM sleep may differ from the process which results in apneas during nonREM sleep.

Based on the finding by other scientists that the 5-HT3 receptor antagonist ondansetron can reduce central sleep apnea, Sigrid C. Veasey et al. postulated that it could be useful for obstructive sleep apnea. In 2001, they compared the effects of two doses (20 mg and 40 mg) of ondansetron on English bulldogs. The 40 mg dose reduced the respiratory disturbance index (RDI) by 50 percent during REM sleep.

Despite these results, scientists see the potential in manipulating the serotonergic pathways of respiration in order to treat apnea and are beginning to develop specially-designed drugs such as the serotonin type 2 5-HT2 receptor antagonist mianserin specifically to reduce sleep apnea. (Mianserin does not yet have FDA approval for this use). Once an effective “apnea pill” is finally developed, people will have another treatment option available if they are unable to tolerate continuous positive airway pressure (CPAP) treatment or unwilling to undergo surgery. 

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Notes

* For more information about the Carley-Radulovacki mirtazapine study, see University of Illinois News Bureau June 2, 2003 Press Release, First Effective Drug for Sleep Disorder Identified, tigger.uic.edu/htbin/cgiwrap/bin/newsbureau/cgi-bin/index.cgi?from=Release&id=602

Bibliography

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Regina Patrick is a freelance writer and registered polysomnographic technologist having worked in the sleep disorders field since 1985. She works for St. Vincent Mercy Medical Sleep Disorders Center in Toledo, Ohio. She is an invited lecturer for sleep technology presentations, and is an associate editor for The A2Zzz. Patrick was last year’s recipient of the APT Dr. Allen DeVilbiss Literary Award.